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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CHEN, STACY BROWN	
ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/498,046	NEIRYNCK ET AL.	
	Examiner	Art Unit	
	Stacy B. Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26,31,32,34,36-41,46 and 52-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26,31,32,34,36-41,46 and 52-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/26/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/26/2007 has been entered. Claims 26, 31, 32, 34, 36-41, 46 and 52-61 are pending and under examination.

Response to Amendment

2. The following rejections are moot or withdrawn in view of Applicant's amendment:

- The rejection of claims 26, 27, 36, 37, 38, 40, 41, 46 and 54-56 under 35 U.S.C. 102(b) as being anticipated by Kurtz *et al.* (U.S. Patent 5,691,189, "Kurtz") is withdrawn in view of Applicant's amendments to the claims.
- The rejection of claims 26, 27, 36, 37, 38, 40, 41, 46 and 54-57 under 35 U.S.C. 103(a) as being unpatentable over Kurtz in view of Sunstrom *et al.* (*J. Membrane Biol.* 1996, 150:127-132, "Sunstrom") is withdrawn in view of Applicant's amendments to the claims.

Claims Summary

3. The claims are drawn to an immunogenic composition comprising a fusion product. The fusion product is comprised of one of the following constructs:

- An antigen comprising an immunogenic extracellular part of an M2 membrane protein of a human influenza A virus and a heterologous presenting carrier.
- An antigen comprising an immunogenic extracellular part of an NB protein of a human influenza B virus and a heterologous presenting carrier.
- An antigen of an immunogenic extracellular part of a CM2 protein of a human influenza C virus and a heterologous presenting carrier.

The presenting carrier is a peptide or polypeptide selected from a hepatitis B core protein, C3d, polypeptides comprising multiple copies of C3d, tetanus toxin fragment C. The fusion product may also be anchored in the membrane of an acceptor cell expressing the fusion product. The fusion product is part of a lipid bilayer or cell wall. The amino acid sequence of the entire extracellular domain is SEQ ID NO: 1, 2 or 3.

New claims 58-61 are drawn to similar constructs as described above, with the exception that the claims include a limitation regarding the process by which the fusion polypeptide is made. Claim 58 indicates that the gene construct that encodes the fusion polypeptide comprises a coding sequence for the immunogenic portion of an influenza virus (A, B or C) linked to a coding sequence for the presenting carrier.

Claim Objections

4. Claim 55 is objected to because it lacks a period at the end of the sentence.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. (*New Rejection*) Claims 26, 31, 32, 36, 38, 41, 46, 53-55 and 58-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pumpens (*Intervirology*, 1995, 38:63-74, "Pumpens") in view of Slepushkin *et al*. (*Vaccine*, 1995, 13(15):1399-1402, "Slepushkin"). Both references were cited in the IDS filed November 26, 2007.

The claims are summarized above. Pumpens teaches that Hepatitis B virus core antigen (HBcAg) particles have been considered ideal epitope carriers for various reasons, including its high-level production and correct self-assembly, its increased immunogenicity (B and T cell responses in primates and rodents) and its flexibility and high capacity for accepting foreign insertions (pages 63-64). While Pumpens does not specifically name influenza virus antigens, it would have been obvious to incorporate any desirable antigen into Pumpens' construct, given the characteristics outlined in Pumpens. Slepushkin discloses that influenza A M2 protein is a transmembrane protein that is highly conserved among human influenza A viruses of different subtypes (page 1399). Also disclosed is that baculovirus-expressed M2, as a subunit vaccine, is able to protect mice against influenza A virus challenge. Slepushkin teaches that vaccinia-M2 recombinants were not able to provide protection in mice when challenged (page 1402, first column, first paragraph). Given that the immunogenicity of M2 alone or in certain constructs is not capable of inducing protective immunity, one would have been motivated to provide a carrier

for the M2 protein that would be able to enhance its immunogenicity, such as the HBcAg carrier taught by Pumpens. One would have had a reasonable expectation of success that the M2 protein expressed together with the HBcAg carrier would have increased the immunogenicity of M2, given the teachings of Pumpens (page 63-64).

With regard to the limitation about the fusion product being a part of a cell wall in claim 38, Pumpens teaches that *E. coli* are widely accepted as the most suitable host for production of chimeric core particles (page 69, first column, second full paragraph).

With regard to the limitation about the inclusion of an adjuvant, Pumpens discloses that the high immunogenicity of HBcAg particles allows the complete exclusion or very restricted use of adjuvants (page 71, first column, last paragraph). It would have been well within the ability of the ordinary artisan to determine whether the use an adjuvant is desirable, and further, which adjuvant is suitable. As is recognized by one of ordinary skill in the art, Freund's adjuvant is toxic in humans. Thus, in the human use context, if one were to have chosen an adjuvant, one would not have chosen Freund's adjuvant.

7. (*New Rejection*) Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pumpens (*Intervirology*, 1995, 38:63-74, "Pumpens") in view of Slepushkin *et al*. (*Vaccine*, 1995, 13(15):1399-1402, "Slepushkin"), as applied to claim 26, and further in view of Highfield *et al*. (AU-B-49273/90, "Highfield", cited in IDS filed 11/26/07). The claim is limited to the fusion product being anchored in the membrane of an acceptor cell expressing the fusion product. Pumpens teaches that *E. coli* is the widely accepted suitable host for production of chimeric core particles. However, it would have been well within the ability of the ordinary

artisan to expression a fusion construct from any acceptable cell line. Highfield discloses the production of HBcAg fusion protein constructs from procaryotic or eucaryotic hosts, including animal cells (page 8, last paragraph, and page 9, last paragraph). Expression of the HBcAg/M2 construct in animal cells would have been expected to produce a fusion protein anchored in the membrane of the animal host cell.

8. (*New Rejection*) Claims 34 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pumpens (*Intervirology*, 1995, 38:63-74, "Pumpens") in view of Slepushkin *et al*. (*Vaccine*, 1995, 13(15):1399-1402, "Slepushkin"), as applied to claim 26, and further in view of Highfield *et al*. (AU-B-49273/90, "Highfield") and van de Guchte *et al*. (*Applied and Environmental Microbiology*, 1989, 55(1):224-228, "van de Guchte"). Claims 34 and 39 require that the immunogenic composition comprise *Lactococci* cells expressing the fusion product in or on their cell membrane or cell well. (*Applicant is requested to clarify if they intend to refer to a cell membrane or cell wall in the context of Lactococci cells which are prokaryotes*.)

The teachings of Pumpens, Slepushkin and Highfield are summarized above. Although Highfield does not specifically suggest the use of *Lactococci* cells for expression of the HBcAg fusion products, it would have been well within the ability of the ordinary artisan to use any appropriate host cell as suggested by Highfield (page 8, last paragraph and page 9, last paragraph). Van de Guchte discloses that lactococcal expression vectors are able to express a wide range of heterologous genes and are generally regarded as safe organisms for hosts (page 224, first column, first paragraph). Given Highfield's suggestion to use any appropriate host, and the general knowledge in the art regarding lactococcal expression vectors, one would have had a

reasonable expectation of success that the use of *Lactococci* cells to produce Pumpens' and Slepushkin's HBcAg/M2 fusion product would have been able to express the fusion constructs.

9. (*New Rejection*) Claims 40 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pumpens (*Intervirology*, 1995, 38:63-74, "Pumpens") in view of Slepushkin *et al.* (*Vaccine*, 1995, 13(15):1399-1402, "Slepushkin"), as applied to claim 26, and further in view of Kedar *et al.* (U.S. Patent 5,919,480, filed June 23, 1997, "Kedar"). Claims 40 and 52 require that the immunogenic composition further comprise an influenza antigen selected from hemagglutinin, neuraminidase, nucleoprotein and native M2, and that the composition further comprise a cytokine, respectively. Pumpens and Slepushkin are silent on the incorporation of other influenza antigens or cytokines into the composition. However, it would have been well within the ability of the ordinary artisan to modify the HBcAg/M2 composition to have a broader immunogenic scope. The incorporation of other known immunogens against influenza would have been obvious, as would the incorporation of an immunostimulating cytokine. Kedar discloses subunit influenza vaccines containing influenza hemagglutinin and neuraminidase in combination with a cytokine (abstract). Although the construct of Kedar differs from Pumpens, the approach to influenza is obviously applicable. Kedar's use of multiple antigens and an immunostimulating cytokine to boost the immune response to influenza would have been expected to increase the breadth of the immune response to the HBcAg/M2 construct of Pumpens and Slepushkin.

10. (*New Rejection*) Claims 26, 31, 32, 36, 38, 41, 46, 53, 54 and 57-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pumpens (*Intervirology*, 1995, 38:63-74, "Pumpens") in view of Slepushkin *et al*. (*Vaccine*, 1995, 13(15):1399-1402, "Slepushkin") as applied to claims 26, 31, 32, 36, 38, 41, 46 and 53-55 above, and further in view of Sunstrom *et al*. (*J. Membrane Biol*. 1996, 150:127-132, "Sunstrom", already of record) or Hongo *et al*. (*Journal of Virology*, April 1997, 71(4):2786-2792, "Hongo").

The claims are summarized above. Pumpens teaches that Hepatitis B virus core particles have been considered ideal epitope carriers for various reasons, including its high-level production and correct self-assembly, its increased immunogenicity (B and T cell responses in primates and rodents) and its flexibility and high capacity for accepting foreign insertions (pages 63-64). While Pumpens does not specifically name influenza virus antigens, it would have been obvious to incorporate any desirable antigen into Pumpens' construct, given the characteristics outlined in Pumpens. Sunstrom discloses that influenza B virus NB protein forms ion channels (abstract). (Influenza B viruses are known to infect humans only, thus the NB protein from influenza B must be a human protein.) Hongo discloses that the Influenza C virus CM2 protein is a transmembrane protein with similar biochemical properties to Influenza A virus M2 and Influenza B virus NB. It would have been obvious to incorporate either NB or CM2 into Pumpens' construct. One would have been motivated to do so by Slepushkin's teaching regarding the M2 protein as an immunization agent. Given that the M2, NB and CM2 are equivalent proteins in terms of being transmembrane proteins that are expressed on infected cells, one would have had a reasonable expectation of success that the incorporation of M2, NB or CM2 into Pumpens' construct would have increased immunogenicity of all proteins. Given

the general construct disclosed by Pumpens and the advantages associated with the HBcAg particles, it would have been well within the ability of the ordinary artisan to incorporate any desired antigen into the construct. Since Slepushkin teaches that M2 is a protein to be used for inducing immunity, and the NB and CM2 proteins are equivalent proteins, it would have been obvious to incorporate NB and CM2 into the Pumpens' construct as well.

Conclusion

11. No claim is allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30), alternate Fridays off,. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Stacy B. Chen/ 2-14-2008
Primary Examiner, TC1600